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(54) Title: INTERFERON GAMMA FOR THE TREATMENT OF ASTHMA

(57) Abstract: The invention describes for the first time the successful clinical application of interferon gamma (IFN-γ) in human bronchial asthma therapy. The clinical data show unambiguously that continuous application of IFN-γ in relatively low doses can be successfully used for long-term treatment of severe asthma bronchiale, especially for glucocorticoid-resistant asthma. The invention relates also to a combination therapy administering IFN-γ and glucocorticoids, which alone are not or not sufficiently effective in asthma therapy.

Interferon Gamma for the Treatment of Asthma

The invention describes for the first time the successful clinical application of interferon gamma (IFN-γ) in human bronchial asthma therapy. The clinical data show unambiguously that continuous application of IFN-γ in relatively low doses can be successfully used for long-term treatment of severe asthma bronchiale, especially of glucocorticoid-resistant asthma. The invention relates also to a combination therapy administering IFN-γ and glucocorticoids, which alone are not or not sufficiently effective in asthma therapy.

Bronchial asthma has been defined by the WHO as "chronic inflammatory disease of the airways" and summarized by chronic infiltration and activation of several types of inflammatory cells in the bronchial mucosa, particularly $CD4^+$ T lymphocytes, defined as helper type 2 phenotype (Th2), by their cytokine profile (Bousquet et al.,1990, *N. Engl. J. Med.* 323:1033–1039; Broide et al., 1991, *J. Allergy Clin. Immunol.* 88:637–648; Robinson et al., 1992, *N. Engl. J. Med.* 326:298–304; Woodley et al., 1994, *Eur. Resp. J.* 7:1576–1584). Chronic inflammation of the respiratory mucosa plays a fundamental role in the pathogenesis of asthma, which affects as many as 10% of individuals in industrialized nations (Roche et al,1989, *Lancet.* 1:520–523). The inflammatory response in asthma is tightly associated with airway hyperresponsiveness, a hall-mark of asthma, and involves a number of different cell types including eosinophils, basophils, mast cells, and, most importantly, Th2 lymphocytes, which can be isolated from the lungs of patients with asthma. When activated, these cells induce mediators of inflammation and cytokines, such as interleukin (IL)-4, IL-5, IL-10 and GM-CSF, which amplify the inflammatory response and may remodel lung architecture. Moreover, IL-13, a pleotropic cytokine produced in large quantities by activated Th2 lymphocytes causes chronic airway inflammation, mucus hypersecretion, subepithelial fibrosis, and eotaxin production (Zhou et al., Z., 1999, *J. Clin. Invest.* 103:779-788), classical features of bronchial asthma. Even more important, abrogation of the IL-13-dependent immune response in IL-13 deficient mouse models led to the complete

abolishment of bronchial hyperresponsiveness (Wills-Karp et al., 1998, *Science* 282: 2258-61; Grünig et al., 1998, *Science* 282:2261-63).

While Th2 cells promote airway inflammation in asthma, it has been proposed that Th1 cells, which secrete IFN-γ, protect against allergic disease by dampening the activity of Th2 effector cells. Th1 cells inhibit the proliferation, and therefore the development, of Th2 cells (Drazen et al, 1996, *J. Exp. Med.* 183:1–5), and IFN-γ inhibits IgE synthesis in some instances (Derdak et al., 1992, *Am. J. Physiol.* 263:L283–L290). For example, it was shown that conventional allergen immunotherapy, which improves symptoms in allergic and asthmatic patients, reduces IL-4 production (Makhluf et al, 1996, *J. Investig. Dermatol.* 107:856–859) and increases IFN-γ production in an allergen-specific fashion (Schmitt-Gräff et al., 1994, *Virchows Arch.* 425:3–24; Phipps et al., 1989, *Am. J. Respir. Cell Mol. Biol.* 1:65–74.). Immunization with IL-12-modified allergen (Schleimer et al., 1992, *J. Immunol.* 148:1086–1092), with heat-killed *Listeria monocytogenes* as adjuvant (Sironi et al., 1994, *Blood.* 84:1913–1921), with intratracheal IL-12, or with naked DNA plasmids containing cDNA for allergens (Bochner et al., 1995, *J. Immunol.* 154:799–803; Wegner et al., 1990, *Science.* 247:456–459) also resulted in a switch in cytokine production in allergen-specific $CD4^+$ T cells and caused a reduction in allergen-induced airway hyperreactivity (Paolieri et al., 1997, *Allergy.* 52:521–531).

Together, these observations suggest that allergen-specific Th1-polarized responses suppress the cellular inflammation characteristic for bronchial asthma. Combined with first clinical results of the inventors, these data present sufficient evidence for conducting a Phase II clinical trial on the therapeutic use of IFN-γ in asthma bronchiale.

Interferon-γ is a naturally glycoprotein having a molucular weight of about 17 kD which can be commercially produced today also by recombinant techniques. Together with (other) cytokines it plays, as already discussed above, an important role within the human immune system, usually showing immunregulatory effects (that means an immunstimulating or an immunsuppressive effect dependent on

cell activation and location). However, there are still outstandimg mysteries about interferons-γ' s complete and real role. What is sure is that it is made in the organism by at least three types of immune system cells (CD4 T helper 1, natural killer, CD8 cytotoxic suppressor) and has effects on at least four different cell types (CD4 T helper 2, macrophage, natural killer, B cell).

As pharmaceutical compound it is used nowadays with a certain success against some viral infections and, above all, against tumors. On the other, hand IFN-γ is, for example, known to be effective alone or in combination with other anti-inflammatory drugs in the treatment of rheumatic arthritis and in inducing production of additional surfactants in the lungs of individuals afflicted with respiratory distress syndrome (RDS). In spite of this knowledge it should be pointed out that – with the exception of tumors – most of the experiences made with IFN-γ are based on in-vitro or animal model data and have no or no sufficient clinical support.

In the context of this invention interferone-gamma was successfully applied in interstitial lung, respectively idiopathic pulmonary fibrosis, disease in combination with prednisolone: the mechanisms that regulate the selected form of immune biology in bronchial asthma are unknown. From investigations performed in the comparable setting of a chronic inflammatory reaction, idiopathic pulmonary fibrosis, which is also characterized by a Th2-polarized immune response, it is known that the clinical application of IFN-g both improves pulmonary function and changes the immune response by reverting the Th2 response(Ziesche et al., 1996, *Chest* 110:25S, EP-A1-0795 332). Moreover, in vivo data on the regulation of cellular function obtained under treatment with IFN-γ in human lung fibrosis suggest that the treatment not only reverts the immunological part of the reaction, but also diminishes the transcription of growth factors tightly associated with the induction of epithelial growth and the regulation of the extracellular matrix, such as transforming growth factor beta1 and connective tissue growth factor (Ziesche et al., 1999, *N. Engl. J. Med.* 341:1264-1269; EP-A1-0795332).

Interferon-γ is usually applicable via parenteral, preferably via subcutaneous, injection. Maximum serum concentrations have been found after seven hours, half life in plasma is six hours.

The main adverse effects consist of fever, chills, sweating, headache, myalgia and drowsiness. These effects have been observed within the first hours after injection. Rare side effects are local pain and erythema, elevation of liver enzymes, reversable granulo- and thrombopenia and cardiotoxicity. No specific antibodies against recombinant interferon-γ have been observed up to now.

The present invention describes now an improved method for the treatment of chronic asthma and, preferably, glucocorticoid-resistant asthma. The term "glucocorticoid-resistant asthma" relates, according to this invention, to asthma forms and asthma-like disorders which are completely or essentially resistant against treatment with glucocoticoids as monotherapy.

Although it is known to negatively affect Th2-like reactions in animal models, there is no hint in the prior art that interferon-γ was ever tried to apply it in the treatment of asthma bronchiale. The invention demonstrates for the first time clinical evidence of IFN-γ in asthma and glucocorticoid-resistant asthma therapy. Although there are partially some unproven and prophetic hints that IFN-γ may be useful in asthma therapy (e.g. WO 87/07842, WO 91/07984) there is no real clinical proof and no exact teaching for a clinical medication of asthma, especially glucocorticoid-resistant asthma. The treatment according to the invention shows significant advantages in contrast to the traditional treatment with high-dosage glucocorticoids or immun-suppressive drugs alone or in combination. The invention shows that - using the drugs mentioned above and below - the symptoms of the disease can be distinctly reduced or mitigated, respectively, the life quality improved. Hard and severe asthma attacks can be diminshed and finally stopped. This can be achieved by applying interferon-γ in low doses and for a long-term period. Surprisingly, the simultaneous application of glucocorticoids , although not effective as monotherapy of glucocorticoid-resistant asthma, causes a positive effect. This effect makes it possible that IFN-γ as well as the glucocorticoid can be administered to the patient in distinctly lower single

and over-all doses. Moreover, the amount of glucocoticoids can be reduced within the first initial phase of the application.

It is shown in the present invention, that the known amounts of IFN-γ which are usually applied in the treatment of viral infections or tumors (approximately 100μg - 5 mg per M^2 of body surface per single dose and per day, up to 7-times per week, e.g. WO 87/07842), can be, as a rule, remained under and have been proven to be efficacious in the treatment of bronchial asthma. It could be further shown that using the drugs indicated below that a long-term treatment is possible which improves distinctly the health and the condition of the patient.

Thus, it is an object of the present invention to provide a new use of low-dosage interferon gamma (IFN-γ) or a combination of low-dosage IFN-γ with glucocorticoids for the manufacture of a medicament or a combination of medicaments for the long-term treatment of bronchial asthma.

It is especially an object of the invention to provide the use of interferon gamma, wherein the bronchial asthma is resistant or essentially resistant against glucocorticoid treatment, if the glucocorticoid is adminstered alone. According to the invention IFN-γ can be used successfully in acute as well as in long-term therapy of bronchial asthma.

It is a further object of the invention to provide a method for a long-term treatment of bronchial asthma in a patient comprising administering interferon gamma (IFN-γ) in low doses or a combination of low-dosage IFN-γ with a glucocorticoid, wherein the period of administration of IFN-γ varies from 4 – 24 months, preferably from 4 – 15 months.

It could be shown that interferon-γ is effective in a dose of 5 – 100 μg, 1- 5 times, preferably 2 – 3 times per week during a period of 4 – 24 months, preferably 10 – 15 months. The above-indicated single dosages of interferon-γ are administered parenteral, preferably subcutaneously to the patient three times per week. Thus, a weekly dosage for a patient is between approximately 15 and 300 μg

interferon. However, it is possible to distribute this weekly dosage among more than three applications.

It is, therefore, an object of the invention to provide a use and method for a long-term treatment of bronchial asthma in a patient comprising administering low-dosage interferon gamma (IFN-γ) or a combination of low-dosage of IFN-γ with a glucocorticoid, wherein a single dose of 5 – 100 μg IFN-γ is administered 1 – 5 times per week.

It is a preferred method and use of the invention, wherein the weekly over-all dose of IFN-γ administered to the patient does not exceed 300 μg.

It is a further preferred object of the invention to provide a corresponding method and use, which comprises a long-term treatment of bronchial asthma in a patient comprising administering low-dosage interferon gamma (IFN-γ), wherein a single dose of 5 – 100 μg IFN-γ is administered 1 – 5 times per week for a period of 4 – 24 months.

As mentioned above the combination of IFN-γ and a glucocorticoid shows advantageous results, since the doses of IFN-γ and glucocorticoid can be reduced without influencing the effect and the term of the treatment even in case of glucocorticoid-resistant asthma. Suitable glucocorticoids are, for example, cortisol, prednisone, cortisone, prednisolone, and 6-α-methylprednisolone. The preferred compound according to the invention is prednisolone.

The doses of glucocorticoids which should be administered to a patient vary according to the invention from 10 - 100 mg / single dose and more preferably from 15 - 80 mg. The initial application is preferably 75 mg.

The glucocorticoid is administered in an initial phase of 1- 4 weeks, preferably 2 – 3 weeks. The dose during this initial dose varies between 20 and 100 mg, preferably 50 – 75 mg. After this initial phase the dose can be reduced to 10 – 5

mg. During the following months of therapy this dose can be continuously cut down and finally stopped.

Thus it is another object of the invention to provide a corresponding use and method wherein the single dose of the glucocorticoid administered during the initial phase of 1 - 4 weeks is 20 – 100 mg, and 10 – 0 mg thereafter.

In general, the optimum therapeutically acceptable dosage and dose rate for interferon-γ and glucocorticoids for a given patient within the above-said ranges depends on a variety of factors, such as the activity of the specific active material employed, the age, body weight, general health, sex, diet, time and route of administration, rate of clearance or the object of treatment.

The term "parenteral" as mentioned above and below includes subcutaneous, intravenous, intra-articular and intratracheal injection and infusion techniques. Oral administration is applicable only in the case of glucocorticoids. This application is not suitable for polypeptides like interferones since they are not bio-available after passing the gastro-intestinal tract.

Interferon is administered preferably in pharmaceutical compositions and formulations which contain beside interferon-γ suitable carriers, excipients, diluents etc. As used herein, the term "pharmaceutically acceptable carrier or excipient" means an inert, non toxic liquid filler, diluent, solvent or solution, not reacting adversely with the active compounds or with the patient. Suitable liquid carriers are well known in the art such as steril water, saline, aqueous dextrose, sugar solutions, ethanol, glycols and oils, including those of petroleum, animal, vegetable, or synthetic origin. The formulations may also contain adjuvants or vehicles which are typical for parenteral administration.

With respect to said suitable formulations it should be pointed out that interferon-γ and glucocorticoids may eventually form pharmaceutically acceptable salts with any non-toxic, organic or inorganic acid showing changed solubility. Inorganic acids are, for example, hydrochloric, sulphuric or phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen

sulfate. Examples for organic acids are the mono, di and tri carboxylic acids such as acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, benzoic, phenylacetic, cinnamic, salicylic and sulfonic acids. Salts of the carboxy terminal amino acid moiety include the non-toxic carboxylic acid salts formed with any suitable inorganic or organic bases. These salts include, for example, alkali metals such as sodium and potassium, alkaline earth metals such as calcium and magnesium, and organic primary, secondary and tertiary amines such as trialkylamines.

According to the invention it is also possible to use IFN-γ in combination with other therapeutically effective agents such as anti-allergic agents, non-steroidal anti-inflammatory or anti-pyretic agents such as phenylbutazone, acetyl salicylic acid, ibuprofen or lipocortins. These agents can be administered in doses and pharmaceutical formulations which are per se known in the art.

Surprisingly, it could be shown that the treatment of asthma patients as indicated above and in the claims has another positive effect. In many cases of chronic asthma the patients develop extensive nasal polyps which cannot be prevented by classical standard therapies like glucocorticoid monotherapy. Therefore, the only possibility to help the patient is surgical removal of the polyps. However, in all cases the nasal polyps redevelop and continue their growth again which leads to a temporary relief only. The method of treating according to the invention has now the effect that redevelopment of nasal polyps after surgical removal can be prevented even after the administration has been finished which is, as a rule, after 12 – 24 months if all severe asthma symptoms are diminished or negligible.

Thus it is another object of the present invention to provide a use and method for preventing redevelopment and continuous growths after surgical removal of nasal polyps associated to asthma and asthma-like diseases comprising administering to a patient IFN-γ or a combination of IFN-γ with a glucocorticoid as indicated above.

Although not yet proven it is a realistic speculation to state that also nasal polyposis induced by other disorders than chronic asthma which undergo similar biological and / or immunological processes or are based on similar inflammatory events can be successfully treated with IFN-γ alone or in combination with steroidal and non-steroidal anti-inflammatory agents.

Investigating the transcription of genes related to the inflammatory mediators TGF-ß1 and IL-13 reveals that there is an increased level of these mediators and a decreased level and even a lack of IFN-γ in tissue of bronchial mucosa of asthma patients. Since these factors are known to be associated with the epithelial growth and its regulation the use with IFN-γ can be speculated to be successful for disorders which show overexpression of said factors.

Therefore, it is another object of this invention to provide a use and method for reducing increased expression of the inflammation mediators IL-13 and TGF-ß1 in bronchial mucosa tissue of asthma patients comprising administering low-dosage IFN-γ or a combination of low-dosage IFN-γ with a glucocorticoid.

In this context, it is also an object of the invention to provide a use and method for treating individuals having increased levels of the inflammation mediators IL-13 and TGF-ß1 in their bronchial mucosa tissue comprising administering IFN-γ or a combination of IFN-γ with a glucocorticoid.

Example 1:

In the following the history of a patient is described with severe, glucocorticoid-resistant extrinsic asthma bronchiale and excessive nasal polyposis who had multiple nasal surgery for a relapse of severe asthma with polyposis that, at the time of the first admission to our outpatient clinic, was complicated by the forth episode of bacterial bronchopneumonia. At this time, the patient had been under oral glucocorticoids (50 mg/day) for more than eight months, combined with full anti-allergic treatment. The course of disease was characterized by frequent

episodes of nocturnal asthma attacks, even during the phases without bacterial exacerbation.

Analysis of gene transcription of relevant mediators of inflammation in the bronchial mucosa of this patient and of two other patients according to the method as described at *Ziesche et al., 1999, l.c.*, revealed a striking lack of IFN-γ with a high transcription of IL-13 and TGF-β1.

Due to the severity of his disease and the imminent danger of a fatal asthma attack, IFN-γ treatment (IFN-γ-1b, Boehringer Ingelheim, Germany) in a dose of 100 μg, 3-times per week was carried out, initially with a combination of oral prednisolone medication (initially 20 mg per day). Additive glucocorticoid treatment was reduced to 7,5 mg per day after three weeks. Figure 2 demonstrates the course of his disease over a period of 12 months under continuous treatment with IFN-γ (300 μg per week) and 7,5 mg prednisolone per day. Meanwhile, the patient has been under IFN-γ treatment for 25 months. Treatment with oral glucocorticoids had been stopped after 14 months of therapy with IFN-γ, and replaced by 1 inhalation of fluticasone dry powder (standard formulation). 14 months after onset of the IFN-γ therapy, the patient underwent again nasal surgery. The extensive nasal polyps were removed. To date, no recurrence has been observed. The undesired effects of IFN-γ treatment had been fever and chills during the first two weeks, and two episodes of headache. All side effects disappeared completely after three weeks of therapy.

The changes in lung volumes (total lung capacity (TLC), functional exspiratory vital capacity (FVC) and functional exspiratory volume (FEV)) and partial pressures of blood gases (pO_2, pCO_2) of the patient during the above-specified treatment are given in Table 1 and Table 2. The FEV1 value increases during the first 12 months from 3,1 l to ca. 4,5 l (+ 48,4 %), the FVC value increases from ca. 4,4 l to 6,5 l (+ 47,7%) and the TLC value increases from 7,1 to 7,6 (+ 7%).

Table 1

months of treatment	0	1	3	6	12
volume (L)					
TLC	7,1	7,0	7,8	7,6	7,5
FVC	4,4	5,2	5,5	6,1	6,5
FEV1	3,1	4,0	3,8	4,6	4,5

Table 2

months of treatment	0	1	3	6	12
mmHg					
pO_2	80	73	74	81	83
pCO_2	25	38	36	37	37

Example 2:

A second case has been followed now for five months. Again, the patient suffered from extrinsic asthma bronchiale, but *without* major nasal polyposis. The initial daily dose of prednisolone was 75 mg. This medication was unable to prevent severe asthma attacks at exertion or during the night. Application of IFN-γ (300 µg per week) together with initially 15 mg prednisolone increased FEV_1 from 2.4 l to 3.1 l. As early as 2 weeks after the beginning of therapy, the patient reported major improvement of exertion capacity.

It is concluded from these individual observations that treatment with IFN-γ may be effectively used with only minor side effects in patients with glucocorticoid-resistant asthma bronchiale.

Patent Claims

1. Use of low-dosage interferon gamma (IFN-γ) or a combination of low-dosage IFN-γ with glucocorticoids for the manufacture of a medicament or a combination of medicaments for the long-term treatment of bronchial asthma.

2. Use of interferon gamma (IFN-γ) according to claim 1, wherein the bronchial asthma is resistant or essentially resistant against glucocorticoid treatment, if the glucocorticoid is adminstered alone.

3. Use of interferon-γ according to claim 1 or 2, wherein the bronchial asthma is accompanied by nasal polyposis.

4. Use according to any of the claims 1 – 3, wherein the single dose of IFN-γ is 5 – 100 μg for administration 1 – 5 times per week.

5. Use according to claim 4, wherein the weekly over-all dose of IFN-γ does not exceed 300 μg.

6. Use according to any of the claims 1 – 5, wherein the single dose of the glucocorticoid in the initial phase of 1 – 4 weeks is 20 – 100 mg, and 10 - 0 mg thereafter.

7. Use according to claim 6, wherein the dose of the glucocorticoide after the initial phase is continuously reduced.

8. Use according to claim 7, wherein the glucocorticoid is prednisolone.

9. Use according to any of the claims 1 – 8, wherein the medicament or the combination of medicaments is provided for adminstration for a period of 4 – 24 months.

10. Use according to claim 9, wherein said period is 4 – 15 months.

11. Use of interferon gamma (IFN-γ) or a combination of IFN-γ with a glucocorticoid for the manufacture of a medicament for the prophylactic prevention of redevelopment and continuous growth of nasal polyps after surgical removal associated to asthma or disorders which are based on similar inflammatory processes.

12. Use of low-dosage interferon gamma (IFN-γ) or a combination of low-dosage IFN-γ with a glucocorticoid for the manufacture of a medicament for reducing increased expression of the inflammation mediators IL-13 and TGF-ß1 in the bronchial mucosa tissue of asthma patients.

13. Use interferon gamma (IFN-γ) or a combination of IFN-γ with a glucocorticoid for the manufacture of a medicament for the treatment of individuals having an increased level of IL-13 and TGF-ß1 in their bronchial mucosa tissue.

14. A method for a long-term treatment of bronchial asthma in a patient comprising administering interferon gamma (IFN-γ) in low doses or a combination of low-dosage IFN-γ with a glucocorticoid, wherein the period of administration varies from 4 – 24 months.

15. A method of claim 13, wherein the period of administration varies from 4 – 15 months.

16. A method for a long-term treatment of bronchial asthma in a patient comprising administering low-dosage interferon gamma (IFN-γ) or a combination of low-dosage of IFN-γ with a glucocorticoid, wherein a single dose of 5 – 100 μg IFN-γ is administered 1 – 5 times per week.

17. A method according to claim 15, wherein the weekly over-all dose of IFN-γ administered to the patient does not exceed 300 μg.

18. A method for a long-term treatment of bronchial asthma in a patient comprising administering low-dosage interferon gamma (IFN-γ), wherein a single dose of 5 – 100 μg IFN-γ is administered 1 – 5 times per week for a period of 4 – 24 months.

19. A method for a long-term treatment of bronchial asthma in a patient comprising administering low-dosage interferon gamma (IFN-γ), wherein the weekly over-all dose of IFN-γ administered to the patient does not exceed 300 μg and the period of administration varies from 4 – 24 months.

20. A method according to any of the claims 13 – 18, wherein the asthma is resistant or essentially resistant against glucocorticoids if administered alone.

21. A method according to any of the claims 13 – 19, wherein the single dose of the glucocorticoid administered during the initial phase of 1 - 4 weeks is 20 – 100 mg, and 10 – 0 mg thereafter.

22. A method of claim 20, wherein the dose of the glucocorticoid is reduced continuously after the initial phase.

23. A method according to any of the claims 13 – 21, wherein the glucocorticoid is prednisolone.

24. A method for preventing redevelopment and continuous growths after surgical removal of nasal polyps associated to asthma and disorders which are based on similar inflammatory processes, comprising administering to a patient IFN-γ or a combination of IFN-γ with a glucocorticoid.

25. A method for reducing increased expression of the inflammation mediators IL-13 and TGF-ß1 in bronchial mucosa tissue of asthma patients comprising administering low-dosage IFN-γ or a combination of low-dosage IFN-γ with a glucocorticoid.

26. A method for treating individuals having increased levels of the inflammation mediators IL-13 and TGF-ß1 in their bronchial mucosa tissue comprising administering IFN-γ or a combination of IFN-γ with a glucocorticoid.